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# THE CARBON DIOXIDE STIMULUS TO BREATHING IN SEVERE EXERCISE

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There has been much speculation for a long time as to the causes of the increased breathing during exercise. In 1905, Haldane & Priestley put forward the theory that it was due to a slight increase in the alveolar $CO_2$ tension ($pCO_2$) and therefore of the arterial $pCO_2$, just as similar increases in alveolar $pCO_2$ induced by $CO_2$ inhalation at rest produced hyperpnoea. Further work showed that whatever might be true for mild exercise, as the work became harder the increase in $pCO_2$ was certainly insufficient to account for the hyperpnoea, and it was clear that some additional factors must come into play. The theory that hydrogen-ion concentration rather than $CO_2$ as such was the stimulus to respiration was more satisfactory since it was known that severe exercise was associated with the accumulation of an excess of lactic acid in the body. Since then, this view has been challenged by many physiologists, and at present there is no agreement as to the main causes of the hyperpnoea. In view of this uncertainty we decided to re-investigate the changes in alveolar $CO_2$ during heavy exercise, together with some factors which might modify the response of the respiratory centre to $CO_2$. The current views are partly based on the contention of Krogh & Lindhard (1913*c*, 1917) that the directly measured alveolar gas tensions do not reflect the gas tensions in the arterial blood during exercise. It is therefore important to the argument presented in this paper that the old controversy between the Danish and Oxford schools of physiology should be re-examined in the light of recent evidence on the alveolar air–arterial blood gas relationships. The arguments used to justify the use of the directly measured alveolar $pCO_2$ as a guide to the arterial $pCO_2$ in exercise are long and intricate and are therefore presented in an appendix to this paper. The conclusions reached are summarized in the main text.

## METHODS

*Alveolar air.* At rest, alveolar air samples were taken by the Haldane–Priestley method. The values presented in this paper were the means of end-inspiratory and end-expiratory samples.

*Automatic alveolar air samples.* In exercise, a modification of the method described by Lindhard (1911), and modified by Rahn & Otis (1949), was used (Fig. 1). In this method the last few c.c. of

each expiration are sampled automatically. The alveolar air was withdrawn continuously at a rate of about 200 c.c./min. It passed from a distribution tap to a sampling tube, to the filter pump and manometer, or to the capillary $CO_2$ meter.

*Calibration of automatic sampling method during hyperpnoea.* In two experiments, during which the subject inspired 6·1 and 7·2% $CO_2$ in air, six comparisons were made between automatic and Haldane–Priestley samples. The inspired air tube was clamped close to the inspiratory valve to prevent leakage through the valve while the sampling tube filled. The methods agreed to within 0·5 mm Hg $CO_2$ tension in all instances. Random differences of similar magnitude were obtained when the methods were compared during severe exercise.

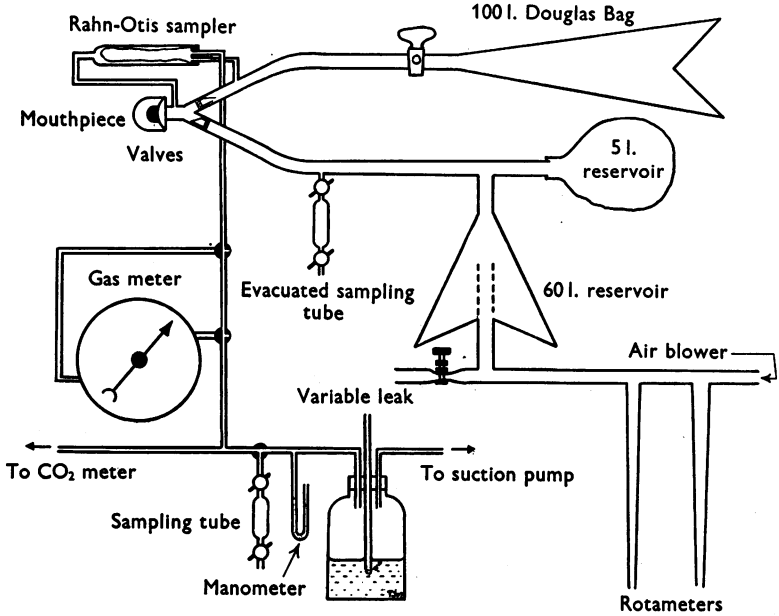


Fig. 1. Apparatus used in exercise experiments. For description, see text.

*Respiratory valves.* It was found that with pulmonary ventilations of 120 l./min (*b.t.p.s.*) the resistance of the conventional Douglas valves imposed a severe strain on the subject. The insertion of a partition between inspiratory and expiratory valves (von Döbeln, 1949) produced no improvement. New low-resistance valves (Bannister & Cormack, 1954) were therefore designed which presented no sudden changes of direction to the flow of air. During standard severe exercise which could not be maintained for more than 9 min without the valves, the breaking point was reached only 1 min earlier when they were worn.

*Carbon dioxide meter.* In the later experiments the alveolar $pCO_2$ was measured with a capillary $CO_2$ meter (Grove-White & Sander, unpublished; Davidson, Hempleman & Trotter, 1951). It required a gas flow of about 80 c.c./min. It was calibrated frequently during each experiment by analysing in the Haldane apparatus samples of the gas flowing into it. It was found to be accurate to about 0·1% $CO_2$.

*Body temperature.* In some experiments the rectal temperature was measured thermoelectrically. The thermocouple was calibrated against a standard thermometer before each experiment.

*Blood lactate.* The lactate content of 0·05 ml. capillary blood was estimated by the method of Barker & Summerson (1941), as modified by Ström (1949). Before taking a blood sample during exercise the subject's finger was wiped carefully to remove sweat. Calibration curves for freshly made up lithium lactate solutions were plotted on each occasion. At the higher values the curves

showed some divergence from day to day. The errors were of the order of 5% of the concentration measured.

*Preparation and supply of gas mixtures other than air.* Inspired gas mixtures other than atmospheric air were supplied to the subject by the method illustrated in Fig. 1. Air and oxygen, or oxygen and nitrogen were passed simultaneously through rotameters calibrated for these gases. Air was supplied from a large electric blower, the fine adjustment of flow being obtained with a controlled air leak. Oxygen and nitrogen were supplied direct from high pressure gas cylinders and flow was regulated by the needle valve on the reducing valve. The three rotameters delivered into a wide tube which passed through a hole in the bottom of an old 60 l. Douglas bag. This served as a reservoir and mixing chamber. It was suspended vertically by its neck and was never allowed to become more than two-thirds full, so that the pressure on the inspiratory side of the apparatus never rose. The neck of the bag opened into a wide bore T-piece which was connected to the inspiratory valve. The other limb of the T-piece led to a 5 l. anaesthetic bag which acted as a supplementary low-resistance reservoir for the inspired gas. Tubing of 1 in. internal diameter was used in these connexions.

*Pulmonary ventilation and respiratory exchange.* These were measured by the bag method, using 100 l. bags. The bags were connected to the expired air tube only a few seconds before an actual determination and were disconnected immediately afterwards, since the three-way taps, when open to the atmosphere, presented a considerable resistance to flow at the rates found, owing to their right angle bend and small lateral orifice. Their resistance was less when the tap was turned to the inside of the bag.

*Respiratory rate.* The respiratory rate remained constant in nearly all experiments. It was always a submultiple of the number of strides per minute. The latter was kept constant for any one subject by setting a metronome to keep pace with his strides at the beginning of a run and asking him to keep pace with it for the duration of the exercise. This he nearly always managed to do without difficulty. The submultiple of the stride rate was determined by observation.

*Exercise.* The subjects ran on a motor-driven treadmill. The platform was 4 ft. 6 in. long. The speed in all experiments was about 6·25 m.p.h. and was measured exactly on all occasions. The intensity of the work was varied by changing the gradient between level and 1 in 6½. The subjects ran in plimsoles and light cotton shorts, with or without thin singlets. Changes of body temperature were kept within bounds by directing a current of air from a powerful electric fan on to the subject.

*Subjects.* Details of the four subjects are shown in Table 1.

TABLE 1. Subjects for experiments

| | | | Maximal exercise maintained for 6–8 min | | | | |
|---|---|---|---|---|---|---|---|
| Subject | Age | Wt. (lb.) | Oxygen consumption (c.c./min) | Gradient | Speed (m.p.h.) | Vertical work (kg m/min) | Athletic ability or occupation |
| R.G.B. | 22 | 154 | 4600 | 1 in 7 | 6¼ | 1650 | International standard miler |
| D.J.C.C. | 30 | 140 | 3200 | 1 in 10 | 6¼ | 1046 | Healthy university demonstrator |
| N.D.McW. | 25 | 152 | 4000 | 1 in 8 | 6¼ | 1430 | International standard sprinter |
| P.J.P. | 36 | 149 | 2900 | 1 in 16 | 6¼ | 700 | Healthy laboratory technician |

*Procedure in exercise experiments.* Before each experiment the exercise valves were checked and assembled, and the Douglas bags were washed out with expired air. The subject gave two resting Haldane–Priestley alveolar air samples and capillary blood was withdrawn for determination of lactate. The subject was instructed to signal the moment he became aware of any major

change in the breathing and then to run until exhausted or until told to stop. During the first 2 min of the run the treadmill speed was adjusted accurately, and in long experiments was checked later from time to time. The alveolar $pCO_2$ was followed by means of the $CO_2$ meter, and from time to time alveolar air was drawn into sampling tubes for subsequent analysis. From the beginning of the third minute samples were taken in the order: capillary blood, alveolar air, and expired air. A complete cycle took, on an average, 2 min, and when the exercise was maximal as many cycles as possible were fitted into the period of the run. With lighter grades of work, the cycles were less frequent in the later stages. At the end of the exercise and at intervals afterwards, capillary blood was withdrawn for estimation of lactate. The subject sat until obvious panting had stopped and then gave Haldane–Priestley alveolar air samples at intervals of about 2 min. Their $CO_2$ content was measured with the meter; this was calibrated by analysis of the first and last alveolar air samples in the Haldane apparatus. The course of a typical experiment is shown in Fig. 2.

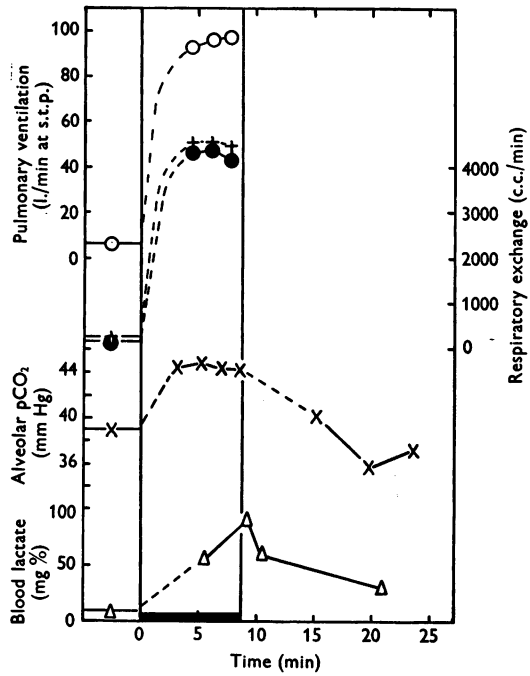


Fig. 2. Exercise experiment. Subject, R.G.B. Speed, 6¼ m.p.h., gradient, 1 in 7. Inspired gas, atmospheric air. +——+, oxygen consumption, c.c./min at s.t.p.; ●——●, $CO_2$ output, c.c./min at s.t.p. Exercise from 0 min to 8 min 45 sec, as indicated by the heavy horizontal line.

*Procedure during $CO_2$ breathing experiments.* The conduct of these experiments was based on those of Campbell, Douglas & Hobson (1914). Mixtures of $CO_2$ in air, made up with rotameters, were stored in 500 and 1000 l. bags. The subject reclined in a deck chair and, after a period of preliminary rest, breathed the mixture for about 20 min. He then gave a Haldane–Priestley alveolar air sample (end-expiration). His expired air was then collected in a bag for measurement of minute volume and $CO_2$ content. The number of breaths required to fill the bag was counted. During this period the inspired air was sampled. After the bag was disconnected the subject gave an end-inspiratory Haldane–Priestley alveolar air sample. This cycle of events was repeated several times. The 'physiological' dead space of the respiratory tract was calculated from the data obtained.

RESULTS

*Changes in the pulmonary ventilation in response to the inhalation of* $CO_2$*–air mixtures at rest.* Addition of $CO_2$ to the inspired air at rest produced the expected changes in pulmonary ventilation in the subjects R.G.B. and D.J.C.C. In Fig. 3 the pulmonary ventilation is plotted against the rise of alveolar $pCO_2$ for these subjects.

*The 'physiological' dead space during* $CO_2$ *hyperpnoea at rest.* The 'physiological' dead space for $CO_2$ was calculated from the data obtained during the experiments on $CO_2$ breathing at rest. The dead space is plotted against the tidal volume in Fig. 4. The lines in this show the relationship between these

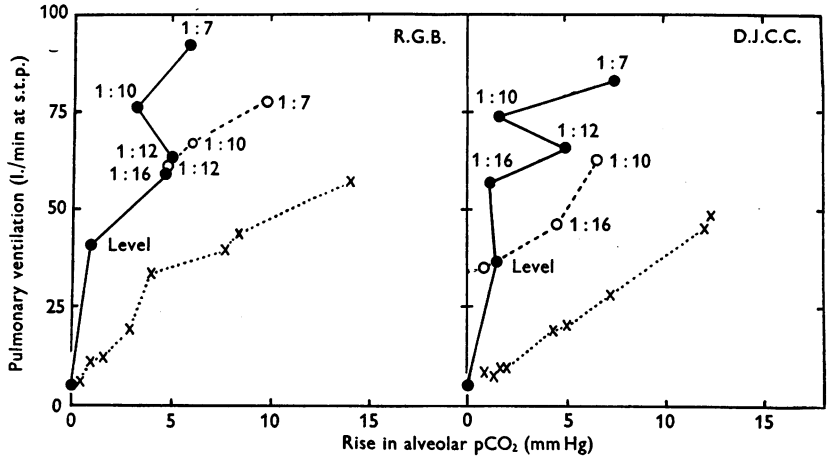


Fig. 3. The pulmonary ventilation and the increase of alveolar $pCO_2$ above the previous resting level. Subjects, R.G.B. and D.J.C.C. Speed in all exercise experiments, 6½ m.p.h. The figures opposite the exercise points indicate the gradient of the treadmill. ●——●, during exercise, breathing atmospheric air; O-----O, during exercise, breathing 66% or 100% $O_2$; ×.....×, sitting at rest, breathing $CO_2$–air mixtures.

variables reported in similar experiments by Campbell *et al.* (1914), by Haldane (1915) during voluntary increases in the depth of the breathing at rest and by Cooper, Emmel, Kough & Lambertsen (1953) during $CO_2$ breathing at rest. Cooper *et al.* calculated the dead space from the Bohr formula, using the arterial instead of the alveolar $pCO_2$. Calculations by us from the data of Houston & Riley (1947) of the dead space during the hyperpnoea at rest of men acclimatized to high altitudes and based, like those of Cooper *et al.* on the arterial rather than the alveolar $pCO_2$ showed average increases of the same magnitude. Our experimental results agree with those of the other workers in showing a considerable increase in the size of the 'physiological' dead space for $CO_2$ at rest when the tidal volume is increased. R.G.B.'s dead space increased threefold when the tidal volume rose from 400 to 1600 c.c.

*The alveolar* $pCO_2$ *and pulmonary ventilation in exercise.* The alveolar $pCO_2$ recorded by means of automatic samples, together with the pulmonary ventilation, respiratory exchange and blood lactate during a typical experiment on severe exercise are plotted in Fig. 2. The alveolar $pCO_2$ during five experiments

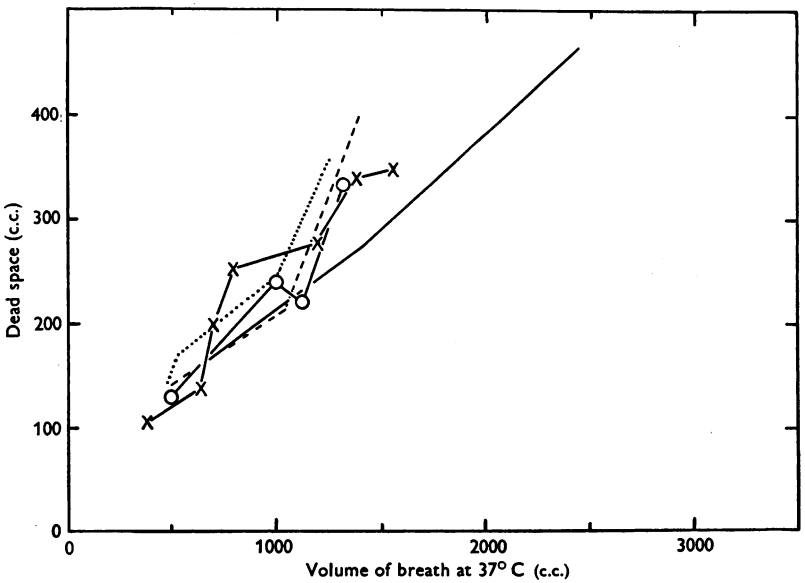


Fig. 4. The 'physiological' dead space at rest. (1) Atmospheric air breathed; tidal volume altered by voluntary variations in respiratory rate; ——, data of Haldane (1915). (2) Inhalation of $CO_2$–air mixtures at rest; ×——×, R.G.B.; O—O, D.J.C.C.; ····, data on C.G.D. (Campbell *et al.* 1914); – – – –, mean for eight subjects, based on arterial $pCO_2$ (Cooper *et al.* 1953).

TABLE 2. Alveolar $pCO_2$, blood lactate and duration of exercise in five identical experiments on R.G.B. Speed 6½ m.p.h., gradient 1 in 7

| Alveolar $pCO_2$ (mm Hg) | | | | | |
|---|---|---|---|---|---|
| | Work | | | | |
| | Time after start (min) | | | Time of stop | Blood lactate after stop |
| Rest (sitting) | 3–4 | 5–6·5 | 6·75–8·0 | min sec | (mg/100 ml.) |
| 40·1 | 46·4 | 46·4 | 45·7 | 8 10 | — |
| 39·5 | 46·2 | 44·8 | — | 8 50 | 90 |
| 38·5 | — | 45·3 | — | 8 15 | 96 |
| 38·7 | 42·9 | 44·9 | 44·9 | 8 10 | 81 |
| 39·1 | 44·5 | 44·8 | 44·3 | 9 45 | 91 |

on the same subject and at the same intensity of exercise are shown in Table 2. The variation between experiments was small. The mean rise of alveolar $pCO_2$ of two subjects during work of varying intensities on a number of occasions are plotted against the pulmonary ventilation in Fig. 3. The results of the experiments on $CO_2$ hyperpnoea at rest are included for comparison. In all the

exercise experiments the alveolar $pCO_2$ rose above the sitting resting values obtained before exercise. When the exercise was severe enough to produce a considerable accumulation of lactate the rise of $pCO_2$ was small and bore no simple relation to the pulmonary ventilation. When the exercise and the lactate production were maximal and the subject was near his breaking point, the alveolar $pCO_2$ showed a further increase. The figure shows that the pulmonary ventilation increased considerably more for a given rise of alveolar $pCO_2$ in exercise than during $CO_2$ inhalation at rest.

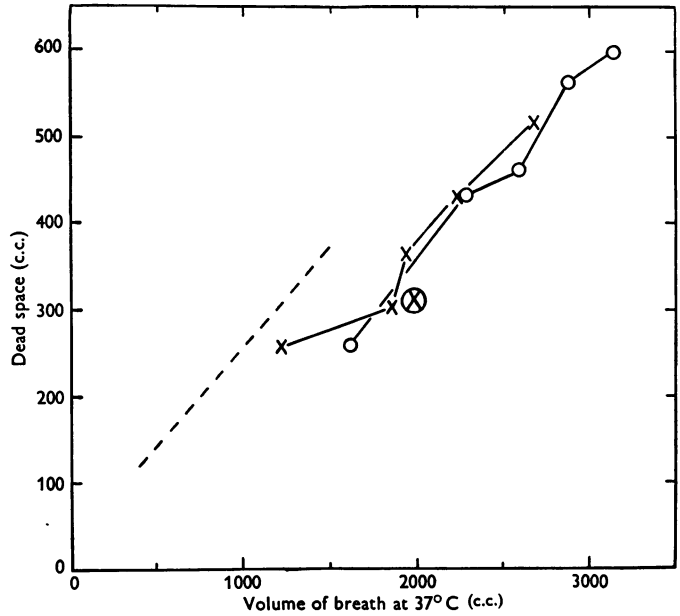


Fig. 5. The 'physiological' dead space during exercise. ×—×, R.G.B.; ○—○, D.J.C.C.; - - - - -, R.G.B.'s dead space at rest during $CO_2$ inhalation (data from Fig. 4); ⊗, a single point in exercise based on the arterial $pCO_2$ (Riley, personal communication).

*The 'physiological' dead space for* $CO_2$ *during the hyperpnoea of exercise.* The 'physiological' dead space for $CO_2$ during exercise was calculated from the data described in the previous section. The values obtained are plotted against the tidal volume in Fig. 5. The figure also shows a line which represents the relationship found for these variables during $CO_2$ breathing at rest, and already presented in Fig. 4. It is clear that the dead space for $CO_2$ increases considerably during exercise, just as it does during the hyperpnoea of $CO_2$ breathing at rest. A single determination of the dead space in exercise by Riley (personal communication) is also shown in the figure. In his experiment, which was representative of many others, the dead space was calculated from the arterial instead of the alveolar $pCO_2$, and, like ours, is considerably larger than the dead space during quiet breathing at rest, though the increase is not quite so

great. We have calculated from the data of Houston & Riley (1947) that the 'physiological' dead space in exercise, based on the arterial $pCO_2$, also shows an increase of the same order as that found in our subjects.

*The alveolar* $pCO_2$ *after exercise.* In order to provide an indication of the threshold to $CO_2$ during exercise, the minimum alveolar $pCO_2$ during the recovery period afterwards was recorded by means of the $CO_2$ meter. The alveolar $pCO_2$ fell to between 29·5 and 36 mm in all experiments, but there was wide variation in the times at which this occurred. An attempt was made to follow two of the factors which might be responsible for this depression, namely, the rise in body temperature and the accumulation of lactate.

In the most severe exercise the highest rectal temperature of about 39° C was recorded after the end of the run. In more prolonged and less severe experiments the rectal temperature was in the region of 39° C after about 10 min and then remained steady at a slightly lower level until the end of the exercise. During the subsequent rest it fell gradually and returned to normal in about half an hour. The rate of fall of temperature seemed to be slower following work of longer duration. The minimum alveolar $pCO_2$ occurred some time after the stop when the body temperature had already fallen considerably.

In another series of experiments, in which the body temperature was not measured, the alveolar $pCO_2$ and the blood lactate concentration were recorded after work of varying severity and duration. The results are shown in Table 3.

TABLE 3. Minimum alveolar $pCO_2$ after exercise of varying duration and severity. Speed in all experiments: 6½ m.p.h.

| Subject | Gradient | Duration of exercise min | sec | Alveolar $pCO_2$ at rest (mm Hg) Before exercise | Minimum after exercise | Time after end of exercise (min) | Blood lactate (mg%) At end of exercise | At time of minimum alveolar $pCO_2$ |
|---|---|---|---|---|---|---|---|---|
| R.G.B. | 1 in 12 | 45 | 0 | 38·0 | 36·0 | 10 | 18 | <14 |
| | 1 in 10 | 41 | 40 | 38·3 | 31·0 | 20 | 26 | <26 |
| | 1 in 7 | 8 | 45 | 39·2 | 35·6 | 11 | 80 | 54 |
| | 1 in 7 | 8 | 10 | 38·7 | 35·1 | 8 | 80 | 72 |
| | *1 in 7 | 15 | 17 | 40·1 | 30·5 | 5 | 60 | 49 |
| | *1 in 7 | 20 | 40 | 39·2 | 29·5 | 20 | 42 | 22 |
| D.J.C.C. | 1 in 16 | 21 | 42 | 40·9 | 34·5 | 12 | 50 | <37 |
| | 1 in 12 | 13 | 15 | 40·3 | 34·0 | 12 | 125 | 95 |
| | 1 in 10 | 8 | 37 | 41·7 | 33·0 | 11 | 155 | 143 |
| | 1 in 10 | 8 | 34 | 40·3 | 34·5 | 6 | 117 | 110 |
| | *1 in 10 | 11 | 20 | 40·4 | 34·5 | 20 | 150 | <140 |
| | *1 in 10 | 20 | 45 | 41·3 | 32·5 | 16 | 100 | 27 |
| | *1 in 10 | 24 | 48 | 40·9 | 30·0 | 10 | 100 | 62 |
| | 1 in 7 | 2 | 31 | 42·0 | 33·2 | 18 | 50 | 130 |

* Denotes oxygen added to inspired air.

There are not enough figures for definite conclusions to be drawn, but certain trends are apparent. At a single intensity of work it seems that the depression of the alveolar $pCO_2$ may have been related to the duration of the exercise

rather than to the blood lactate concentration. This may have been an effect of changes of body temperature. The magnitude of the depression appeared to be related to the blood lactate only in the three experiments on R. G. B. which lasted for more than 20 min, but even in these the body temperatures may not have been identical. However, in D.J.C.C. the duration of the depression appeared to be proportional to the accumulation of lactate. The time when the minimum alveolar $pCO_2$ occurred varied greatly. There was no obvious explanation for this.

*The effects on the alveolar* $pCO_2$ *of inspiring* 66 % $O_2$ *in* $N_2$ *during exercise.* In experiments to be described in the following paper (Bannister & Cunningham, 1954) the subjects inspired 66 % $O_2$ in $N_2$ during the exercise. The body temperature and blood lactate during the subsequent rest were followed in some of these experiments. Amongst other effects, the pulmonary ventilation was reduced when the work was of considerable severity and the alveolar $pCO_2$ rose to higher levels than those recorded when the subjects breathed atmospheric air. This finding is illustrated in Fig. 3. In the subject N. D. McW. it rose to the unusual value of 55 mm Hg. Three readings of 50 mm or more were recorded in the case of R. G. B. Values up to 48 mm were found with the other two subjects.

*The onset of the hyperpnoea.* In several experiments our subjects were aware of a relatively small increase in the ventilation right at the start of the exercise. Between 45 and 60 sec later, a sudden increase to a much higher level was apparent. It was not measured, but the subject signalled when he noticed the onset of this secondary rise. It usually occurred over the space of about half a dozen respiratory cycles. It corresponded in time to rapid changes in the alveolar $pCO_2$ as measured by the $CO_2$ meter. Cunningham & Douglas (unpublished) have observed that the lactate in capillary blood shows no change until 45–60 sec after the start of work, when, if the exercise is of sufficient severity, it starts to increase rapidly. These findings are in agreement with those of Hickam, Pryor, Page & Atwell (1951).

## DISCUSSION

In these experiments the alveolar gas tensions were measured on the grounds that they indicated the arterial gas tensions, particularly that of $CO_2$. Similar measurements have frequently been made in the past, but there are few reports of experiments on sustained exercise of the severity performed by our subjects.

The values reported here, like the earlier determinations, are open to the criticism that they may differ by a considerable margin from the arterial gas tensions. Some justification for their continued use must therefore be given. There have been comparatively few direct comparisons of the arterial and

alveolar gas tensions in exercise (Dill, Lawrence, Hurxthal & Bock, 1927; Dill, Edwards, Fölling, Oberg, Pappenheimer & Talbott, 1931; Riley, Lilienthal, Proemmel & Franke, 1946; Galdston & Wollack, 1947; Suskind, Bruce, McDowell, Yu & Lovejoy, 1950). Only one series was performed during exercise of any severity. The results are conflicting and will be considered in an appendix to this paper. An indirect approach must therefore be attempted.

The size of the respiratory dead space is crucial to the problem since it is closely connected by the Bohr formula with the alveolar gas tensions. It is well known that the 'physiological' dead space, calculated from the alveolar gas tensions, when these are measured directly, increases considerably during exercise. However, Krogh & Lindhard (1913*a*, 1917) measured it by an independent method and found that it changed very little. The calculated alveolar gas tensions which resulted from their values for the dead space were practically the same as those prevailing during rest. They concluded that the directly measured alveolar gas tensions, on which the large dead spaces were based, differed considerably from the arterial gas tensions, and that changes of arterial $pCO_2$ were quite insufficient to account for the hyperpnoea of exercise and played only a minor part in its production. This view is now widely accepted (Nielsen, 1936; Comroe, 1944; Gray, 1950). However, Haldane & Priestley (1935*a*) believed that the dead space, when measured by this independent method, was not applicable to the problem of the alveolar and arterial tensions of the physiologically active gases.

There are now sufficient experimental data for a tentative choice to be made between these divergent points of view. The argument is long and complex and has therefore been presented in an appendix to this paper. The conclusion is reached that the only way to settle the matter finally is to make direct comparisons between the arterial blood gas tensions and those of the alveolar air sampled by the different methods. This has been done at rest, but not to any extent during exercise. There are at least three different concepts of the alveolar air and the dead space. They are all correct in themselves and when applied to the appropriate problems. The method of sampling which probably reflects most closely the arterial blood gas tensions at rest and the arterial $pCO_2$ in exercise is that of Haldane & Priestley (1905) or some other method based on the same principle. The 'alveolar expired air' of Krogh & Lindhard (1913*c*, 1917) is probably misleading when applied to the problem of respiratory control.

*The contribution of change in arterial* $pCO_2$ *to the hyperpnoea of exercise.* Of recent years most writers on this subject have been sceptical about the part played by changes in arterial $pCO_2$ in the production of exercise hyperpnoea, in particular because it was thought that the directly determined values for alveolar $pCO_2$ were too high and that the indirect method of Krogh & Lindhard gave more reliable results. For example, Comroe (1944) thought that such

changes in $pCO_2$, if present at all, were too small to be of much significance. The demonstration by Barcroft & Margaria (1931) that the minute volume during exercise might be nearly twice that found when breathing high concentrations of $CO_2$ supported this view. This opinion is widely held (Pitts, 1949; Gray, 1950) and has resulted in a search for the 'missing factor'. Some years ago it seemed likely that afferent impulses from the working limbs (Harrison, Calhoun & Harrison, 1932; Comroe & Schmidt, 1943; Asmussen, Christensen & Nielsen, 1943) or impulses from the cerebral cortex (Krogh & Lindhard, 1913*b*; Nielsen, 1936) might be important. However, even the most extensive and rapid passive movements gave only small changes of minute volume. Even when the slight acapnia which resulted from the hyperpnoea was partially corrected by the inhalation of $CO_2$, only two- or three-fold increases were obtained, as compared with the 20-fold increases recorded in maximal work (Bahnson, Horvath & Comroe, 1949; Otis, 1949). However, for the reasons outlined in the preceding section, we think that the rise of alveolar $pCO_2$ during exercise at the intensities studied indicates that a comparable rise of $pCO_2$ occurred in the arterial blood (Fig. 3). Lilienthal, Riley, Proemmel & Franke (1946) measured the arterial $pCO_2$ by a direct method before and during exercise. In moderate exercise they found an average increase of about 3 mm when the pulmonary ventilation was about 30 l./min. In one subject doing work which was almost as severe as that done by our subject D.J.C.C., the arterial $pCO_2$ was 3 mm above its resting value when the ventilation was 57 l./min. The increase is slightly greater than that found by us. Suskind *et al.* (1950) found an increase of 5 mm in the arterial $pCO_2$ above the standing resting level after 4 min of very light work. The pulmonary ventilation was increased to 11 l./min. Hickam *et al.* (1951) observed an increase from 43·3 at rest to 48·2 and 47·6 mm during the fourth and ninth minutes of exercise respectively, when their eleven untrained subjects performed fairly hard work on a treadmill. These increases were not quite significant and varied considerably from one individual to the next. The arterial pH was decreased. Morgan & Grodins (1950) and Grodins & Morgan (1950) working on anaesthetized dogs whose hind limbs were stimulated electrically, found no significant change in the arterial $pCO_2$ or pH when the steady state was reached except in acutely spinal animals. Their experiments are open to four main criticisms:

(1) Grodins (1950), when commenting on the experiments of Asmussen *et al.* (1943), postulated the existence of muscle receptors which respond only to abnormal concentrations of anaerobic products. These might well be activated by direct electrical stimulation.

(2) It is well known that in anaesthetized animals at rest anoxic stimulation of the carotid body contributes to the maintenance of respiration. This would be at least as important in exercise, but Morgan & Grodins have not considered it as a possible factor.

(3) Anaesthetics depress the respiratory response to $CO_2$ (von Euler & Söderberg, 1952).

(4) Animals suffering from spinal shock are not good preparations for the investigation of the magnitude of normal responses. In the circumstances their experiments cast little light on the occurrences in unanaesthetized exercising human subjects.

Asmussen & Nielsen (1946) reported a rise of alveolar $pCO_2$ which was smaller than that recorded here. Their measurements were based on the use of a nearly constant dead space and so would underestimate the change. They also demonstrated a fall in alveolar $pCO_2$ when the exercise became severe and when atmospheric air was inspired. We found a relative depression under comparable conditions, but when the intensity of work was increased to maximum values the alveolar $pCO_2$ showed a further increase. Asmussen & Nielsen attributed the fall in alveolar $pCO_2$ to the release of a hypothetical respiratory stimulant which they said was produced by ischaemic muscles and which was not lactic acid. We agree that another factor related to want of oxygen, which is not lactate accumulation, contributes to the hyperpnoea of heavy exercise, but we regard their evidence for a specific respiratory stimulant as inconclusive. This point is discussed more fully in a subsequent paper (Bannister & Cunningham, 1954).

However, even during less severe exercise, in which lactate was produced in small amounts only, the increase in alveolar $pCO_2$ from its resting value was considerably less than that required to produce similar changes in pulmonary ventilation during $CO_2$ breathing at rest. There are three possible explanations for this: (1) the sensitivity of the respiratory centre to changes of alveolar $pCO_2$ (i.e. the response per unit change of stimulus) was increased several fold (2) the threshold to the $CO_2$ stimulus was lowered, or (3) $CO_2$ was not a factor in the exercise hyperpnoea. Different meanings have been attributed to the word 'threshold'. Nielsen (1936) determined the ventilatory response to changes of alveolar $pCO_2$ during $CO_2$ inhalation under a variety of circumstances. The response curves were extrapolated back to zero ventilation and the corresponding values of $pCO_2$ were taken as the 'thresholds'. They are the apnoea points of other workers. For many years in this laboratory 'threshold' has meant the level of alveolar $pCO_2$ which would exist during natural breathing at rest, and corresponds approximately to Nielsen's 100% $pCO_2$ stimulus at rest. For the present purpose the argument is the same whichever meaning is intended.

Factors which might lower the 'threshold' or alter the sensitivity to $CO_2$ in exercise may be of two classes, those which act only for the duration of the exercise and those which persist for some time afterwards. The first group includes nervous influences such as reflexes from muscles and joints and, in severe exercise, the direct or indirect effects of oxygen lack. In heavy exercise

nervous influences can be assessed only indirectly as it is impossible either to imitate passively the movements of running uphill or to abolish the afferent pathways in man. The effects of want of oxygen may be abolished by allowing the subject to breathe air enriched with oxygen. Asmussen & Nielsen (1946) showed that this procedure during heavy work reduced the pulmonary ventilation and allowed the alveolar $pCO_2$ to rise to higher levels. Our findings are in agreement with this. When the results of the exercise experiments in which 66% oxygen was inhaled are substituted in Fig. 3 for the results of the air breathing experiments, the slope of the curve relating ventilation to change of alveolar $pCO_2$ approaches that of the $CO_2$ sensitivity curve at rest. However, the difference is still large and requires further discussion.

The factors which persist for some time after exercise include changes in the body temperature and in blood lactate. Haldane (1905) showed that the pulmonary ventilation at rest was increased and the alveolar $pCO_2$ lowered by rises of body temperature. Bazett & J. B. S. Haldane (1921), Bazett (1924) and Landis, Long, Dunn, Jackson & Meyer (1926) showed that subjects immersed in baths hot enough to cause a rise of rectal temperature experienced a considerable hyperpnoea and their alveolar $pCO_2$ fell to low levels. They attributed this in part to temperature reflexes from the skin. Data on this point are scarce, but it is reasonable to suppose that the threshold to $CO_2$ is lowered when the body temperature rises; if the alveolar $pCO_2$ were suddenly raised to normal levels by the addition of $CO_2$ to the inspired air, severe panting would result. Christensen (1931) and Asmussen & Nielsen (1947) have reported substantial increases in rectal temperature during exercise, compared with which our figures are rather low.

Temperature change as a major factor in the production of exercise hyperpnoea was doubted by Comroe (1944) on the grounds that it took place too slowly. We would agree that the rise in body temperature is too slow to act as a primary stimulus, but from the results presented here, together with the data of Haldane (1905) and of Landis *et al.* (1926), it seems likely that this rise will have become sufficient to depress considerably the threshold to $CO_2$ 10 min after the start of the exercise. Most of the determinations of alveolar $pCO_2$ during exercise have been made more than 5 min after the start in order to ensure steady state conditions, and it is generally believed that measurements earlier than this are of doubtful value. The original determinations of alveolar $pCO_2$ by Haldane & Priestley (1905) and by Douglas & Haldane (1912) were made within 5 or 6 min of the start; so also were the measurements of arterial $pCO_2$ by Lilienthal *et al.* (1946) and by Suskind *et al.* (1950). In the experiments on light and moderate work reported by these investigators, lactate production was probably minimal and changes of body temperature were slight at the time when the measurements were made. The threshold for

$CO_2$ would therefore be almost unaltered, and it is significant that the rise of alveolar $pCO_2$ reported by Haldane & Priestley and Douglas & Haldane and of arterial $pCO_2$ by Lilienthal *et al.* and by Suskind *et al.* above the previous resting level went a long way towards explaining the observed hyperpnoea on the $CO_2$–H ion theory of breathing. However, in the experiments on heavy exercise which they reported the relationship no longer held, since enough time had elapsed for a considerable amount of lactate to accumulate.

The relationship between the alveolar $pCO_2$ during recovery after heavy work and the blood lactate concentration was recognized long ago (Christiansen, Douglas & Haldane, 1914; Hill, Long & Lupton, 1924). The depression of alveolar $pCO_2$ which we observed was similar to that found by Christiansen *et al.* but smaller since our exercise was more prolonged and the lactate changes less acute. In some of our experiments changes of body temperature may have been greater. Dill *et al.* (1927) found that the arterial $pCO_2$, measured directly, dropped abruptly after exercise to about 10 mm below the value obtained during the work. They did not account for this. Barr & Himwich (1923) and Hickam *et al.* (1951) made similar observations on the arterial $pCO_2$. J. B. S. Haldane, Linder, Hilton & Fraser (1928) and Nielsen (1936) have shown that comparable reductions in the alveolar $pCO_2$ occur at rest during $NH_4Cl$ acidosis. In our exercising subjects the blood lactate increased to 10 or 15 times the resting values and the pH changes in the venous blood (Bannister, 1952) were of the same order as those produced by Nielsen. Our experiments were not designed to separate the effects of changes of temperature and lactate but merely to show that they were sufficient to account for the depression of the alveolar $pCO_2$. When it reached its lowest value the lactate and temperature disturbances had already subsided considerably.

The conventional point from which to assess the stimulus due to changes of $pCO_2$ in exercise is the alveolar $pCO_2$ measured during the preliminary rest. However, a more reasonable figure would be the minimum value of the alveolar $pCO_2$ after exercise. This concept is illustrated in Fig. 6. The dotted line shows the course of the alveolar $pCO_2$ which would be expected from the $CO_2$ theory of breathing if there were no change in threshold, i.e. if no other factor participated in the response. The observed change in ventilation should be produced by the large increment $X$ in the alveolar $pCO_2$. Such an increase would result from the inhalation of 6·5 or 7 % $CO_2$ at rest, a concentration usually regarded as unphysiological. It is found experimentally that the alveolar $pCO_2$ undergoes only a trifling rise, $Y$, which is quite insufficient to account for the increase in ventilation. After exercise the alveolar $pCO_2$ falls to levels well below the previous resting value. Evidently a degree of hyperpnoea persists for some time afterwards, probably as a result of the continued influence of the excess lactate and the higher body temperature which developed during the work. In other words, the threshold for the $CO_2$ stimulus

to the respiratory centre has fallen below the normal level because other stimuli are operative in addition. Such a reduction of threshold must operate during the exercise since the lactate and temperature disturbances are the result of the exercise and are more severe during it. If during the depression, $CO_2$ were added to the inspired air to bring the alveolar $CO_2$ back to the normal resting, or even to the exercise value, a large hyperpnoea should result. In preliminary experiments of this type, enough $CO_2$ was inhaled

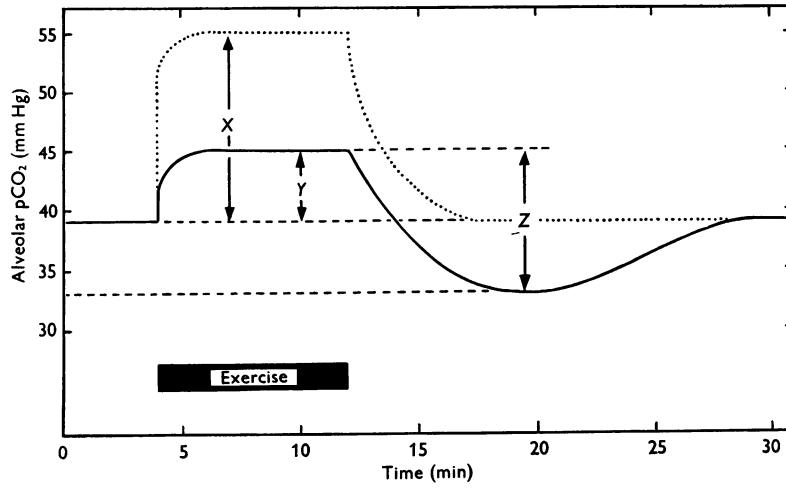


Fig. 6. Diagrammatic representation of the course taken by the alveolar $pCO_2$ before, during and after severe exercise. ....., course predicted on $CO_2$ theory of breathing; ——, observed course. *X*, change of $pCO_2$ required by $CO_2$ theory of breathing; *Y*, observed change of $pCO_2$ from previous resting value; *Z*, change of $pCO_2$ above post-exercise minimum value. For explanation, see text.

during the recovery period to raise the alveolar $pCO_2$ to the level found during the preceding exercise. The resulting ventilations were very much greater than those produced by the inhalation of the same $CO_2$-air mixtures before the exercise. They were, in fact, almost comparable to those recorded during the exercise (Fig. 7). If we wish to relate the change in ventilation to the alteration of alveolar $pCO_2$ it would be more rational to estimate the latter, not by comparison with the normal resting level, but with the minimum value which occurs after the exercise. Account is thus taken of the lowered threshold to $CO_2$ which is clearly present at the time when the minimum $pCO_2$ during recovery is recorded and which must also have been operative during the preceding exercise. On this basis the true $pCO_2$ stimulus would be *Z* in Fig. 6. Even this may be an underestimate since some lactate is eliminated and the temperature begins to fall during the few minutes intervening between the end

of the exercise and the time when the alveolar $pCO_2$ reaches its lowest level. The erect posture during the work might depress the threshold further as it does at rest (e.g. Suskind *et al.* 1950). This factor has not been included in our assessments of the $pCO_2$ stimulus.

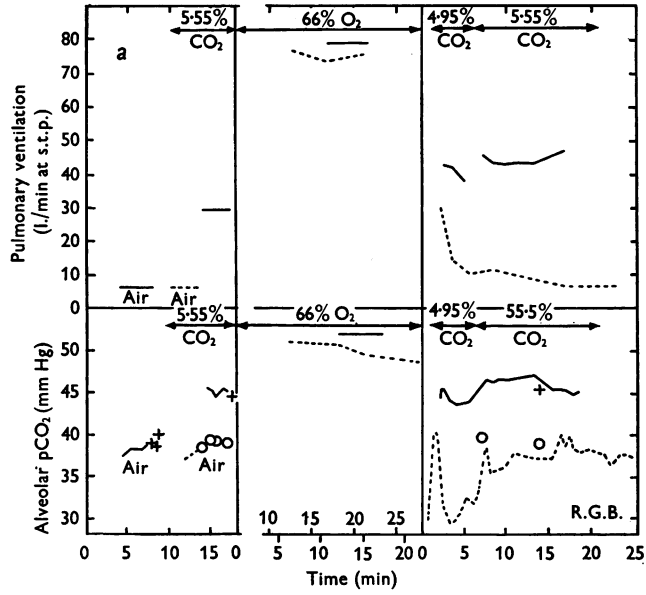


Fig. 7*a*. Effect of inhalation of $CO_2$ before and after severe exercise. Subject, R.G.B. Two experiments at the same intensity of exercise (6½ m.p.h. up a gradient of 1 in 7). - - - - -, control experiment, during which air was breathed during rest and recovery, and 66% $O_2$ during exercise. ——, test experiment, during which air, then 5·55% $CO_2$ was breathed at rest; 66% $O_2$ during exercise; during recovery, air was breathed for the first minute, followed by 4·95% $CO_2$ until the end of the 5th minute, followed by 5·55% $CO_2$ for the remainder of the experiment. O, +, alveolar $pCO_2$ by Haldane–Priestley method during the control and the test experiments respectively. All other $pCO_2$ values by the Rahn–Otis method. In both experiments, the blood lactate concentration at the end of exercise was between 25 and 30 mg/100 ml. Note that the respiratory response to 5·55% $CO_2$ was greater after exercise than before it. This did not approach the exercise value since the inspired $CO_2$ concentration was insufficient to raise the alveolar $pCO_2$ during recovery to the exercise level.

Fig. 8 shows the relationship between the pulmonary ventilation and the $pCO_2$ stimulus calculated in this way. The dotted line is the curve obtained at rest when breathing various concentrations of $CO_2$ in air. The full lines join the points obtained during air-breathing experiments, and the dashed lines those which resulted when 66% oxygen was inhaled during the exercise. In the latter experiments any possible interference from arterial anoxaemia was avoided. From this it will be seen that the ventilation and the alveolar $pCO_2$ in exercise are related in a manner not unlike that found during $CO_2$ inhalation at rest.

It is beyond the scope of this paper to suggest how $pCO_2$ and pH changes interact in their effects on the breathing. The acidosis resulting from the presence of an excess of circulating lactate would add to the hyperpnoea which resulted from the $CO_2$ stimulus. On the $CO_2$-H ion theory they are merely different aspects of

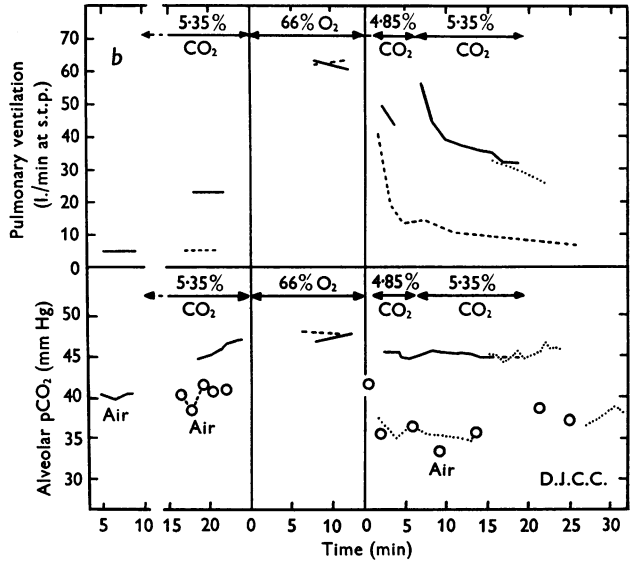


Fig. 7*b*. Effect of inhalation of $CO_2$ before and after severe exercise. Subject, D.J.C.C. Two experiments at the same intensity of exercise (6½ m.p.h. up a gradient of 1 in 11). – – – –, control experiment, during which air was breathed during rest and recovery, and 66% $O_2$ during exercise. ——, test experiment, during which air, then 5·35% $CO_2$ was breathed at rest; 66% $O_2$ during exercise; during recovery, air was breathed for the first minute, followed by 4·85% $CO_2$ until the end of the 6th minute and 5·35% $CO_2$ for the remainder of the experiment. O, individual points for alveolar $pCO_2$ by Haldane–Priestley method at rest breathing air. During $CO_2$ breathing and exercise, $pCO_2$ by Rahn–Otis method. ....., recovery period during a preliminary experiment at the same intensity of work. $pCO_2$ by Rahn–Otis method throughout. Air breathed for first 14 min of recovery, 5·35% $CO_2$ from 15th to 23rd minute and air from 24th minute onwards. Ventilation measured only during $CO_2$ breathing in this experiment. In all experiments, the blood lactate concentration was between 70 and 85 mg/100 ml. at the end of exercise. Note that 6 min after the exercise, raising the alveolar $pCO_2$ almost to its exercise level resulted in a pulmonary ventilation at rest almost as great as was found in exercise, in contrast to the small response to the same alveolar $pCO_2$ before exercise. This augmentation of the response decreased rapidly.

the same stimulus. We have deliberately omitted any discussion of the effect and nature of the stimulus arising from want of oxygen as it will be the subject of another paper. When the effects of oxygen want are present, as is the case when exercise of this severity is performed breathing atmospheric air, the $CO_2$ stimulus is slightly smaller. This is more than compensated for by the anoxia and the pulmonary ventilation is considerably greater. A lowered threshold to $CO_2$ was postulated by Nielsen (1936) to account for the effects of $CO_2$

inhalation during exercise. He attributed it chiefly to nervous influences from the cerebral cortex or from the working limbs. In a later paper Asmussen & Nielsen (1946) minimized the importance of these nervous factors in heavy exercise but it was not clear how much of the hyperpnoea was to be attributed to the lowering of the threshold to $CO_2$. Presumably the 60 l./min which they measured when oxygen want was abolished would, on their theory, be partly explained by nervous stimulation of the respiratory centre.

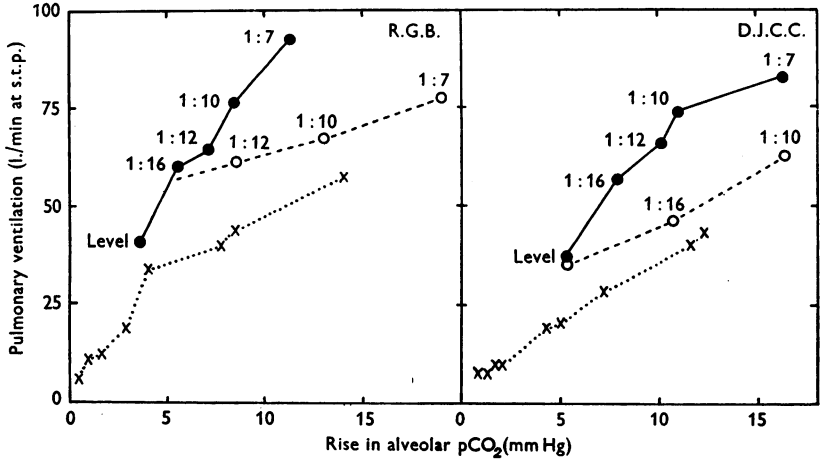


Fig. 8. The pulmonary ventilation and the increase of the alveolar $pCO_2$ above the minimum value recorded during recovery after the exercise. Points based on the data already presented in Fig. 3. Subjects, R.G.B. and D.J.C.C. Speed in all exercise experiments, 6½ m.p.h. The figures opposite the exercise points indicate the gradient of the treadmill. ●—●, during exercise, breathing atmospheric air; ○—○, during exercise, breathing 66% or 100% $O_2$; ×—×, sitting at rest, breathing $CO_2$-air mixtures.

Our experiments were not directly concerned with the factors responsible for the hyperpnoea of light exercise. We are unable to assess directly the contribution of nervous factors in heavy work, but agree with Asmussen & Nielsen (1946) in assigning to them only a minor role. When the direct or indirect effects of oxygen want are abolished by the inhalation of 66% $O_2$ the pulmonary ventilation is not much greater than that which is caused by the inhalation of high concentrations of $CO_2$ at rest and the effective $pCO_2$ stimuli are comparable in the two cases. We think, therefore, that the missing factors in the production of hyperpnoea in severe exercise are want of oxygen, acting either directly or indirectly, and a lowering of the threshold of the respiratory centre to $CO_2$ as a result of the acidosis and the changes of body temperature. By this means the ventilatory response to a given level of arterial $pCO_2$ is much increased. We have found no evidence for an increase in the sensitivity of the respiratory centre to $CO_2$, but our data are insufficient to exclude it.

SUMMARY

1. Two athletes and two non-athletic subjects ran on a motor-driven treadmill up various gradients. Alveolar $pCO_2$, pulmonary ventilation, respiratory rate and blood lactate were measured before, during and after the exercise. In some experiments rectal temperature was recorded.

2. The ventilatory response and alveolar $pCO_2$ of two of the subjects were determined at rest when varying concentrations of $CO_2$ were added to the inspired air.

3. In all instances during exercise the alveolar $pCO_2$ rose to levels above those found during the preceding rest. The rise was less marked during fairly severe than during lighter exercise. In maximal exercise, the alveolar $pCO_2$ rose to levels well above those found during lighter work.

4. When oxygen was added to the inspired air during submaximal and maximal exercise, the alveolar $pCO_2$ rose to higher levels than when air was breathed.

5. The curve relating change of alveolar $pCO_2$ to pulmonary ventilation when oxygen want was abolished in this way was almost parallel to that found during $CO_2$ inhalation at rest, but was some distance from it. It was concluded that $CO_2$ by itself was unable to account for the hyperpnoea. This was no doubt attributable in part to the accumulation of excess lactate and to the raised body temperature.

6. After exercise, the alveolar $pCO_2$ fell to levels well below those recorded during the preliminary rest. This depression was attributed to the persistence of the acidosis and the elevation of the body temperature which had occurred during the exercise.

7. When the $CO_2$ stimulus was estimated as the difference between the alveolar $pCO_2$ during exercise and the minimum value recorded during recovery, and this difference was plotted against the pulmonary ventilation, the resulting curve had the same slope as that obtained during $CO_2$ inhalation at rest, and was only slightly above it.

8. In preliminary experiments on two subjects, 5·5% $CO_2$ was inhaled during recovery at the time which corresponded to the maximum depression of the alveolar $pCO_2$ in the earlier experiments. The resulting ventilations were much greater than those recorded during $CO_2$ inhalation at rest when this was not preceded by exercise. In one subject the values so obtained were comparable with those found during the exercise.

9. It was concluded that the accumulation of lactate and the raised body temperature together depressed the threshold of the respiratory centre to $CO_2$ and that these three factors combined would account for the greater part of the hyperpnoea of severe exercise when the possibility of arterial anoxaemia was avoided by adding oxygen to the inspired air. When atmospheric air was

breathed, an additional stimulus connected with want of oxygen appeared to be involved.

10. The 'physiological' dead space of the respiratory tract was calculated for the hyperpnoea of exercise and of $CO_2$ breathing. In both conditions it increased considerably with the tidal volume. The increases were of similar magnitude to those recorded by other investigators who used the arterial instead of the alveolar $pCO_2$ for calculating the dead space.

11. In an appendix to the paper, recent work on the alveolar-arterial blood gas relationships was considered, together with some of the earlier concepts. It was concluded that the directly measured alveolar $pCO_2$ during exercise probably reflected the arterial $pCO_2$ more closely than the alveolar $pCO_2$ values calculated from the expired $CO_2$% and an almost fixed 'anatomical' dead space.

## APPENDIX

### *The alveolar air, respiratory dead space and the arterial blood gas tensions*

*Quiet breathing at rest.* Haldane & Priestley (1935*a*) were interested in the alveolar air as an indication of the arterial blood gas tensions and believed that the mean of the end-inspiratory and end-expiratory samples approximated most closely to these. They thought that the composition of the alveolar air might vary considerably in different parts of the lungs, but showed that with a deep expiration a remarkably uniform plateau for $pCO_2$ and $pO_2$ could be obtained once the dead space had been washed out. They considered that a variable part of the axial stream in the respiratory bronchioles (Miller, 1947) would contribute to the 'physiological' dead space, which could therefore have physiological definition only. The whole of the air in the atria and respiratory bronchioles would be excluded from the 'anatomical' dead space, as measured by inert gases. This concept required that the air from these relatively hyperventilated regions, which would be expelled in the early part of a deep expiration, should have a high R.Q., and therefore the R.Q. of the remainder would be lower than that of the mixed expired air. The fractional analyses of single breaths by Aitken & Clark-Kennedy (1928), and by Hitchcock & Stacy (1950) using the mass spectrometer show that this is so. The Haldane–Priestley method has been criticized recently by Rahn (1949). He has, however, misunderstood the method in that his samples were delivered over a period of 2–3 sec. Haldane insisted that the samples should be delivered quickly and forcefully, and that the end of the alveolar air tube should be blocked as soon as the deep expiration was over.

Krogh & Lindhard (1917) criticized the Haldane–Priestley method because of the uncertainties underlying the assumption that the mean of the two samples was the mean for the alveolar air. DuBois, Britt & Fenn (1952) have recently investigated this point. Krogh & Lindhard maintained that the average composition of the alveolar air, which they termed the 'alveolar expired air', could best be obtained by calculation from the composition of the expired air and the volume of the 'anatomical' dead space, as measured with an inert gas. Their values for the dead space determined in this way have been confirmed by Fowler (1948) and Lilly (1950) using the nitrogen wash-out technique. Pappenheimer, Fishman & Borrero (1952) have recently introduced a novel method for estimating the dead space and alveolar gas tensions. Their concept is, as far as we can see, entirely sound and results in the correct measurement of the 'anatomical' dead space and the 'alveolar expired air' of Krogh & Lindhard, i.e. all the gas which takes an active part in the respiratory exchange.

Riley *et al.* (1946) and Riley & Cournand (1949, 1951) have introduced the concept of the 'effective' or 'ideal' alveolar air, based on the arterial $pCO_2$ measured directly, and the R.Q. of the expired air. This alveolar air would be the same as that of Krogh & Lindhard (1917) and of

Pappenheimer *et al.* (1952) only under a unique set of circumstances which are unlikely to be fulfilled in the lungs, and which will be considered below. The differences between the dead spaces and alveolar airs obtained by all these methods are small during quiet breathing.

TABLE 4. Comparison between arterial and alveolar $CO_2$ tensions when these are measured simultaneously

$\Delta$ = (alveolar-arterial) $pCO_2$.

| Observer | No. of observations | Oxygen consumption (c.c./min) | $pCO_2$ (mm Hg) Arterial | Alveolar: Haldane–Priestley End-insp. Value | End-insp. $\Delta$ | Haldane–Priestley End-exp. Value | End-exp. $\Delta$ | End-normal expiration Lindhard; Henderson; Rahn & Otis Value | $\Delta$ |
|---|---|---|---|---|---|---|---|---|---|
| I. Rest | | | | | | | | | |
| Bock & Field (1924) | 15 | — | 38·8 | — | — | 38·3 | −0·5 | — | — |
| Dill *et al.* (1927) | 20 | — | (assumed = HP end-exp.) | — | — | 40·9 | — | 36·6 | −4·3 |
| Bock *et al.* (1929) | 10 | — | 41·75 | — | — | 41·5 | −0·2 | — | — |
| Dill *et al.* (1931) (high altitude) | 4 | — | 31·6 | — | — | 30·9 | −0·7 | — | — |
| Riley *et al.* (1946) | 20 | — | 35·5 | 39·9 | +4·4 | — | — | — | — |
| Galdston & Wollack (1947) | 9 | — | 42·0 | — | — | 41·0 | −1·0 | — | — |
| Barker *et al.* (1949) | 33 | — | 40·5 | 38·7 | −1·8 | 40·7 | +0·2 | 38·6 | −1·9 |
| Suskind *et al.* (1950) | 10 | — | 36·0 | — | — | — | — | 33·8 | −2·2 |
| II. Exercise | | | | | | | | | |
| Dill *et al.* (1927) | (*a*) 7 | *c.* 1400 | 39·9 | — | — | 41·5 | + 1·6 | — | — |
| | (*b*) 9 | *c.* 1400 | 40·2 | 40·2 | 0·0 | — | — | — | — |
| | (*c*) 14 | *c.* 1700 | (assumed = HP end-insp.) | 42·0 | 0·0 | — | — | 42·0 | 0·0 |
| Dill *et al.* (1931) (high altitude) | 5 | 2210 | 30·3 | 29·9 | −0·4 | — | — | — | — |
| Lilienthal *et al.* (1946) | 11 | 1500 | 34·6 | 47·3 | +12·7 | — | — | — | — |
| Galdston & Wollack (1947) | 11 | *c.* 1550 | 41·0 | — | — | 44·0 | +3·0 | — | — |
| Suskind *et al.* (1950) | 10 | *c.* 1000 | 41·5 | — | — | — | — | 43·5 | +2·0 |

In 1911 Lindhard introduced a method for sampling the last few c.c. from the end of a series of normal expirations. Campbell, Douglas, Haldane & Hobson (1913) criticized it on the grounds that the dead space would be inadequately washed out during quiet breathing. Henderson & Haggard (1925) and Rahn & Otis (1949) have introduced automatic devices acting on the same principle, and which would therefore be expected to suffer from the same defect during quiet breathing. Recent experiments in this laboratory suggest that this error may be considerable when standard respiratory valves are used. However, with a special valve the dead space of which is only 11 c.c., it becomes quite small.

A number of direct comparisons between the alveolar and arterial $pCO_2$ both at rest and during exercise have been summarized in Table 4. Rahn's (1949) series at rest has not been included since the experimental data are not available and since, as mentioned above, his tracings indicated that he did not appreciate the details of the Haldane–Priestley method. However, he found that the arterial $pCO_2$ and the alveolar $pCO_2$ measured by his automatic end-normal expiration method

were in close agreement. The results, except those of Riley *et al.* (1946), agree in showing that at rest the Haldane–Priestley end-expiratory sample gives a value very close to that for the arterial $pCO_2$. The end-normal expiration method of Lindhard (1911), Henderson & Haggard (1925) and of Rahn & Otis (1949), and the Haldane–Priestley end-inspiratory sample tend to give low values for $pCO_2$. Barker, Pontius, Aviado & Lambertsen (1949) used a refined version of Riley's syringe method for measuring arterial gas tensions. Their findings agreed with those of the earlier workers. For $pCO_2$ there was little difference between the various methods though the end-normal expiration method of Rahn & Otis (1949) and the end-inspiration Haldane–Priestley sample gave low values. The Rahn–Otis method had the smallest standard deviation. In addition, they found that for oxygen all methods except the Haldane–Priestley end-expiratory sample gave values higher than the arterial $pO_2$. Lambertsen (personal communication) found that the R.Q.'s of all samples were the same as the expired air R.Q., except that of the Haldane–Priestley end-expiratory sample, which was low. Since, however, this method reflects more closely the arterial gas tensions than any of the others, it follows that the R.Q. of the hypothetical sample whose gas tensions are identical with those found in the arterial blood will also be low. Calculations by us from Lambertsen's data show that this R.Q. is lower even than that by the Haldane–Priestley end-expiratory method. It also follows that Rahn's (1949) criticism of the Haldane–Priestley method on the grounds of its low R.Q. should in reality be a criticism of the other methods when they are judged by the accuracy with which they reflect the arterial blood gas tensions.

Variations in the ratio of ventilation to blood-flow (termed in the U.S.A. the ventilation-perfusion ratio) in different parts of the lungs will explain these discrepancies in gas tensions and R.Q., as was pointed out by Haldane & Priestley (1935*b*) and discussed recently by Riley & Cournand (1949, 1951) and by Rahn (1949). The results of such inequalities will show themselves in two ways. First, by definition, there is a surplus of gas and a deficit of blood in the over-ventilated regions, and the opposite is true where there is underventilation and excessive blood flow. The equilibrium values for $CO_2$, when compared with that established in evenly ventilated and perfused regions, will be low in the first case and high in the second. It follows that, even if the dissociation curve for the gas in question is linear, the average tensions found in the whole of the gas and blood phases will differ from each other since the gas phase will be weighted towards the low value found in the overventilated regions while the blood phase will incline towards the high value of the over-perfused areas. Secondly, when the dissociation curve of the gas is not linear there will be a further difference of gas tension between the whole alveolar air and the mixed arterial blood in addition to that resulting from the spatial factors outlined above. The reasons for this were clearly described by Haldane & Priestley (1935*b*). The values for both $CO_2$ and oxygen will be affected equally by the spatial factors. Those for $CO_2$ will scarcely be affected by the shape of the dissociation curve, since it is almost linear over the physiological range. At atmospheric pressure breathing air, the relevant part of the oxygen dissociation curve is far from linear and so will aggravate the discrepancy. One would therefore expect the difference for oxygen to be greater than that for $CO_2$. It follows that the R.Q. of the hypothetical alveolar air sample whose gas tensions are equal to those of the arterial blood will be lower than that of the expired air. It also follows that the 'physiological' dead space for oxygen calculated from this sample will be larger than that for $CO_2$. All three conditions are closely fulfilled by the end-expiration sample of Haldane & Priestley when this is correctly delivered, as may be shown from the data of Barker *et al.* (1949).

The existence of these inequalities of distribution of blood and gas to different parts of the lung seems to be fairly well established. Much has been written about the 'effective venous shunt' across the pulmonary circulation which results from the anatomical arrangements of the bronchial and Thebesian veins and variations in the ventilation-perfusion ratios in different parts of the lungs. However, there has been little mention recently of the overventilated regions in the smaller air passages. Miller (1947) described alveoli lining the terminal bronchioles, whose main function appeared to be the conduction of gases. He called them the respiratory bronchioles. Further on were the atria where air conduction also seemed relatively more important than gas exchange. From his diagrams it is clear that these alveoli would be grossly overventilated during inspiration.

The first air out of the lungs proper during expiration would come from them and should show evidence of a high ventilation-perfusion ratio. Haldane, Meakins & Priestley (1918) described the effects of this arrangement particularly during rapid shallow breathing. The physiological confirmation of their views came from the fractional analyses of single expirations performed during exercise by Aitken & Clark-Kennedy (1928) and at rest by Hitchcock & Stacy (1950). They found that the early fractions had R.Q.'s in excess of unity, and that subsequently the R.Q. fell to values lower than that of the mixed expired air. One may therefore say that an obligatory overventilation occurs in these regions just as an obligatory addition of venous blood may occur on the left side of the heart. The magnitude of these obligatory inequalities of ventilation and perfusion has not been clearly established. It appears that the essence of the old controversy between the Oxford and Copenhagen schools of respiratory physiology was whether the gas coming from the overventilated regions should be included in the dead space or the alveolar air. Probably both views were correct when used in the right contexts.

It seems to us that there are at least three different types of alveolar air sample, each related to the expired air by its own dead space.

(1) The 'alveolar expired air' of Krogh & Lindhard and of Pappenheimer *et al.* (1952) includes all the gas which takes part in the respiratory exchange. It will not have the same gas tensions as the arterial blood unless the ventilation and perfusion ratios are absolutely uniform all over the lung; if this were so, it would also agree with the other two methods of sampling alveolar air. If inequalities exist, the 'alveolar expired air' will have a lower $pCO_2$ and higher $pO_2$ than any of the other samples. The corresponding dead space will be the 'anatomical' dead space and will be smaller than the others. The R.Q. will be the same as that of the expired air.

(2) The 'ideal' alveolar air of Riley and co-workers has, by definition, the $pCO_2$ of the arterial blood. Since the spatial factors mentioned above are applicable to the values of $pCO_2$, it follows that this method corrects for them, both for $CO_2$ and oxygen. In addition, the non-linearity of the dissociation curve will apply for the oxygen values at sea-level breathing air, and so under these conditions the 'ideal' alveolar air will have a $pO_2$ higher than that of the arterial blood. Both the oxygen and $CO_2$ values will be related to the expired gas composition through the 'physiological' dead space for $CO_2$ which during quiet breathing is slightly larger than the 'anatomical'. The R.Q. is, by definition, that of the expired air.

(3) In our view the end-expiration sample of Haldane & Priestley corrects empirically for both sets of factors and thus gives values close to the arterial gas tensions for both gases. The correction results from exclusion of that part of the 'alveolar expired air' which comes from the overventilated regions. The Haldane–Priestley dead space for $CO_2$ will equal that for 'ideal' alveolar air and will be the 'physiological' dead space for $CO_2$. Their 'physiological' dead space for oxygen will be larger still. The R.Q. will be lower than that of the expired air.

All these alveolar air samples have their own particular uses. For example, the 'ideal' alveolar air of Riley and co-workers and the end-normal expiration methods of Lindhard (1911) and of Rahn & Otis (1949) do not depend on the active co-operation of the subject and so avoid subjective errors. During quiet breathing the differences between the results obtained by the different methods are fairly small. Perhaps Lindhard's end-normal expiration sample should be avoided during quiet breathing unless apparatus of minimal dead space is used or unless an empirical correction factor is applied.

*Hyperpnoea.* During hyperpnoea, particularly when the breathing is rapid, it becomes increasingly difficult to distinguish between the end-inspiratory and end-expiratory Haldane–Priestley samples. The increased tidal volume washes out the dead space more effectively so that the objection to the Lindhard method is no longer valid. With extreme hyperpnoea the three methods become indistinguishable except that the Lindhard method gives the average of a number of respiratory cycles and so is preferable. During exercise and during $CO_2$ breathing we compared the $pCO_2$ obtained by the Lindhard method and by sampling the end of a maximal expiration. We were unable to detect any systematic difference between the two.

Direct comparisons between arterial and alveolar $CO_2$ tensions during exercise are summarized in Table 4. The data are not numerous and may be used in support of either Krogh's or Haldane's

view. In favour of the latter, it may be said that the determinations by Dill, Hurxthal, van Caulaert, Fölling & Bock (1927) at rest have been largely confirmed by other workers and the same methods were used by Dill *et al.* (1927) in exercise. Under these conditions they found the Haldane–Priestley end-inspiratory sample and the automatic method of Henderson & Haggard (1925) to be the most reliable. The method of obtaining Haldane–Priestley samples used by Riley *et al.* (1946) for some reason gave much higher values at rest than those used by other workers; one would expect the difference to be magnified in exercise. Galdston & Wollack (1947) collected their samples during the minute following exercise when rapid fluctuations in $CO_2$ levels would be occurring. Exact timing was of extreme importance and they admitted to slight delays in sampling in some instances. Nevertheless, their end-expiratory samples did not show a much greater discrepancy than those of Dill *et al.* (1927). We would agree tentatively with Dill *et al.* that the evidence, such as it is, favours the Haldane–Priestley end-inspiratory sample and others like it during exercise.

Since there are so many uncertainties we are forced back to the indirect argument involving the dead space. The $pCO_2$ of an alveolar sample which gives a dead space which is nearly the same as that calculated from the arterial $pCO_2$ during hyperpnoea obviously cannot differ very much from the arterial $pCO_2$ itself. Samples of this type are therefore the most suitable for studies on respiratory control.

The difference between the results for the dead space obtained by these methods and by the indirect methods of Krogh & Lindhard and of Pappenheimer *et al.* (1952) becomes large and of great importance during hyperpnoea. The 'physiological' dead space as calculated from the composition of the alveolar air when sampled directly, increases considerably during hyperpnoea. Douglas & Haldane (1912) found this for exercise, Campbell *et al.* (1914) for the hyperpnoea of $CO_2$ breathing at rest and Haldane (1915) and Henderson, Chillingworth & Whitney (1915) for deep slow breathing at rest. However, Krogh & Lindhard (1913*a*, 1917) found that the 'anatomical' dead space, as measured by Siebeck's hydrogen method (1911) did not increase very much during deep breathing either at rest or during exercise. Their results have been confirmed by Fowler (1948) and Lilly (1950) using nitrogen as the test gas, and by Pappenheimer *et al.* (1952). Krogh & Lindhard (1917) criticized the results of Henderson *et al.* (1915) on apparently valid grounds. They also pointed out that the values for alveolar $pCO_2$ in exercise on which the dead spaces reported by Douglas & Haldane (1912) were based were too high owing to the accumulation of $CO_2$ in the lungs during the delay which occurred in sampling by the Haldane–Priestley method. They calculated that this factor would account for the whole of the difference between the two sets of results. Haldane & Priestley (1935*a*) admitted the error, but their calculations suggested that it was much smaller than Krogh & Lindhard had thought. Krogh's criticisms of Haldane's results obtained during quiet breathing were equivocal, and they failed altogether to explain the results of Campbell *et al.* (1914), in which there was no increase in the rate of $CO_2$ production. Douglas & Havard (1932) showed that the Haldane–Priestley method of sampling, which in 1914 had resulted in a big increase in Douglas' 'physiological' dead space during $CO_2$ hyperpnoea at rest, also gave a correct value under the same conditions for his arterial $pCO_2$ since the arterial pH calculated from it agreed with that determined by the glass electrode. Recently, Cooper *et al.* (1953) have shown that the 'physiological' dead space when calculated from the directly measured arterial $pCO_2$ increases during a $CO_2$ hyperpnoea by about the same amount as claimed by Campbell *et al.* (1914). Our results also agree with those of Campbell *et al.* (Fig. 4). Furthermore, Riley (personal communication) has shown that this is true for exercise when the arterial $pCO_2$ is used in the Bohr equation. Our calculations from the data of Houston & Riley (1947) bear this out. Our results in exercise also show a considerable increase, which is slightly greater than that of Riley (Fig. 5), but no greater than that of Houston & Riley. The results of Pappenheimer *et al.* (1952) show that Haldane's data (1915) may be used to calculate the 'anatomical' as well as the 'physiological' dead space during deep breathing.

Fractional sampling of an expiration has not yet thrown much light on the controversy. It was first performed by Krogh & Lindhard (1913*c*), but their methods have been questioned by Aitken & Clark-Kennedy (1928). These authors gave values for the dead space during exercise which were

intermediate between those of Krogh & Lindhard and of Campbell *et al.* (1914). They in turn have been criticized with some justification by Nielsen (1936). It should be added that the alveolar $pCO_2$ which would result from the dead space calculated by Aitken & Clark-Kennedy or by Nielsen would be that existing at the beginning of the alveolar $pCO_2$ plateau, and would therefore be lower than the mean alveolar $pCO_2$. The techniques of fractional analysis used by Hitchcock & Stacy (1950) have not, to our knowledge, been used during the hyperpnoea of exercise or of $CO_2$ inhalation at rest, but Kydd (1950) has shown that the dead space is greatly increased during voluntary and involuntary hyperventilation.

On these grounds we have formed the opinion that during hyperpnoea the 'physiological' dead space for gases which are actively exchanged increases considerably, but the true, or 'anatomical' dead space of Krogh & Lindhard (1913*a*, *c*, 1917) undergoes comparatively little change. The recent experiments using arterial blood as a standard are in support of this view, as are the experiments on the washout of nitrogen during oxygen breathing by Fowler (1948) and by Lilly (1950). In the absence of an adequate number of direct comparisons between arterial and alveolar $pCO_2$ during exercise uncertainties must remain, but it is apparent that one of the direct methods of alveolar air sampling will give results closer to the arterial values than those involving the use of a nearly constant dead space in the Bohr formula. The situation regarding the values for $pO_2$ in arterial blood and alveolar air is less clear, but that is not the concern of this paper. We therefore decided to use the Haldane–Priestley method for samples taken during quiet breathing and the Lindhard method as modified by Rahn & Otis (1949) for hyperpnoea.

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